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Biphasic Changes in Left Ventricular End-Diastolic Pressure During Dynamic Exercise in Patients With Nonobstructive Hypertrophic Cardiomyopathy

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OBJECTIVES The aim of this study was to clarify the serial changes in left ventricular (LV) end-diastolic pressure (LVEDP) during dynamic exercise in patients with hypertrophic cardiomyopathy (HCM).

BACKGROUND Although HCM is characterized by impaired resting LV diastolic function, serial changes in LVEDP during exercise have not been characterized.

METHODS We simultaneously measured LV pressure and LV dimensions during symptom-limited supine bicycle exercise in 5 healthy individuals and 20 patients with HCM. Exercise thallium-201 scintigraphic studies were also performed.

RESULTS The LVEDP (baseline: 12 ± 5 mm Hg) progressively increased to a maximum value at peak exercise (28 ± 8 mm Hg) in 11 patients with HCM (group I). In the remaining nine patients with HCM (group II), changes in LVEDP during exercise were biphasic, with an initial progressive increase and a subsequent gradual decline up to peak exercise (14 ± 4 mm Hg at baseline, 27 ± 5 mm Hg at the critical heart rate, 16 ± 3 mm Hg at peak exercise). Exercise-induced changes in LV dimensions and LV peak systolic pressures were similar in both groups. However, the maximum first derivative of LV pressure was greater and the LV pressure half-time was shorter in group II than in group I at a similar peak exercise heart rate. The biphasic changes in LVEDP disappeared by pretreatment with propranolol. The LV hypertrophy scores were higher in group I than in group II. Exercise thallium-201 images showed more severe perfusion defects in group I than in group II patients.

CONCLUSIONS The biphasic changes in LVEDP seen during exercise may be related to improved coronary microcirculation in response to beta-adrenergic stimulation in patients with mild to moderate HCM. (J Am Coll Cardiol 2001;38:335–43) © 2001 by the American College of Cardiology

Left ventricular (LV) diastolic dysfunction in patients with hypertrophic cardiomyopathy (HCM) is characterized by an increased resistance to diastolic filling associated with impaired relaxation, reduced LV compliance and increased resting LV filling pressures (1). However, LV diastolic performance, especially in late diastole, during dynamic exercise has not been fully evaluated in patients with HCM.

Because increases in LV end-diastolic volume are usually accompanied by increases in LV end-diastolic pressure (LVEDP), the LVEDP may serve as an index of LV diastolic function. However, the LVEDP may be elevated without an increase in LV end-diastolic volume because of diminished ventricular compliance in the setting of ischemia, hypertrophy, fibrosis and infiltrative diseases of the ventricle and in pericardial disease (2,3). Animal studies have demonstrated that LVEDP increases markedly during exercise in the chronically pressure-overloaded hypertrophied canine LV (4,5). Serial changes in LVEDP during dynamic exercise, however, have not been fully characterized in patients with HCM. The aim of the present study was to determine the relationship between LVEDP and the intensity of supine bicycle exercise. Therefore, we simultaneously measured central and systemic hemodynamics by right and left heart catheterization and LV dimensions by echocardiography during symptom-limited supine bicycle exercise.

METHODS

Study group. We studied 20 patients (mean age: 51 years) with newly diagnosed nonfamilial, nonobstructive HCM. All patients had evidence of LV hypertrophy on electrocardiograms (ECGs) and echocardiograms. None of the patients had previously taken cardioactive medications. All patients were in normal sinus rhythm and had a normal LV ejection fraction by left ventriculography (mean: 70 ± 9%; range: 55% to 87%). Incidence of HCM was diagnosed using established clinical, hemodynamic and echocardiographic criteria (6). No significant intraventricular pressure gradient was detected either at rest or during exercise in any patient with HCM as assessed by Doppler echocardiography. The control group consisted of five patients (mean age:

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Abbreviations and Acronyms

^{201}Tl	= thallium 201
ANOVA	= analysis of variance
ECG	= electrocardiogram
EDD	= end-diastolic dimension
ESD	= end-systolic dimension
HCM	= hypertrophic cardiomyopathy
HR	= heart rate
LV	= left ventricular
LV dP/dt_{max}	= the maximum first derivative of LV pressure
LVEDP	= left ventricular end-diastolic pressure
SPECT	= single-photon emission computed tonography
$T_{1/2}$	= LV pressure half-time

57 years) who had been referred for evaluation of atypical chest pain. All patients in the control group had normal ECGs, left ventriculograms and echocardiograms. None of the patients had valvular heart disease or >50% narrowing of the coronary arteries by coronary arteriography.

The patients with HCM were grouped according to the changes in the LVEDP in response to dynamic exercise. Group I consisted of 11 patients in whom the LVEDP increased progressively with increases in the intensity of exercise up to peak exercise. Group II consisted of nine patients in whom the LVEDP changes were biphasic, with an initial progressive increase (ascending limb) and a subsequent gradual decline (descending limb). We defined the critical heart rate (HR) as the HR at which the LVEDP reached a maximal value during progressive increases in dynamic exercise. The study protocol was approved by our Institutional Review Committee. Written, informed consent was obtained from all patients.

Simultaneous ECG, echocardiography and catheterization. Right and left heart catheterization was performed using the brachial approach in fasting patients as previously described (7). An externally balanced and calibrated 6F pigtail angiographic micromanometer-tipped catheter (model SPC-464D, Millar Instruments, Houston, Texas) was used to measure LV pressure. The signal from the micromanometer was adjusted to match that of the catheter. A 21-gauge cannula was used to measure the arterial pressure. The ECGs were recorded using the Mason-Likar modification of the standard 12-lead ECG. Micromanometer pressure signals and ECGs were recorded simultaneously and continuously with a multichannel recorder (MR-40, TEAC Corp., Tokyo, Japan). Echocardiography was performed with a Hewlett-Packard (Andover, Massachusetts) model Sonos 2500 ultrasound system equipped with a 2.5-MHz transducer. The LV pressure, ECG and phonocardiogram were recorded simultaneously with the LV short-axis M-mode echocardiogram on a strip chart at a paper speed of 100 mm/s. Echocardiographic data were measured and the degree of LV hypertrophy was determined semiquantitatively as previously described (7).

Hemodynamic study. After baseline data were obtained, patients performed a symptom-limited supine bicycle ergometer exercise test according to a previously described method (7,8). The initial workload was 25 W (150 kpm/min) and increased by 25 W every 3 min. We were unable to obtain clear echocardiographic recordings at workloads >50 W, probably because of an increase in the air content of the lungs. Therefore, we analyzed echocardiographic data during exercise at a workload of 50 W. Representative recordings of the ECG, LV pressure and the M-mode echocardiogram in a patient with HCM at baseline and during 50 W of exercise are illustrated in Figure 1. During exercise, no patients developed a new outflow tract pressure gradient or greater than mild mitral regurgitation by Doppler echocardiography.

Hemodynamic study with propranolol. After the exercise study had been completed, four of the nine patients with HCM, who showed biphasic changes in LVEDP during exercise, were randomly selected to receive an intravenous injection of propranolol (0.1 to 0.12 mg/kg). Fifteen to 30 min after injection, the exercise protocol was repeated.

Scintigraphic study. Exercise thallium-201 (^{201}Tl) images were obtained using a single-photon emission computed tomographic (SPECT) method two days before catheterization. A symptom-limited exercise test was performed while patients were seated on a bicycle ergometer using the same exercise protocol as in the hemodynamic study noted in the preceding text. Thallium-201 (111 MBq) was injected intravenously 1 min before the exercise was stopped. Stress imaging was performed 10 min after exercise and rest imaging was performed 3 h later. The ^{201}Tl SPECT images were obtained with a rotating two-head gamma camera (ECAM, Toshiba Inc., Tokyo, Japan) equipped with a low-energy, high-resolution parallel-hole collimator. Tomographic slices (6 mm thick) were reconstructed for the vertical long-axis, horizontal long-axis and short-axis.

Determination of plasma catecholamine concentrations. Blood (5 ml) was collected from the brachial artery at rest and at peak exercise. Plasma samples (3 ml) were stored at −70°C until the time of assay. The plasma concentrations of norepinephrine were analyzed by high-performance liquid chromatography.

Hemodynamic data analysis. The LV pressure signals were digitized at 3-ms intervals and analyzed with software developed in our laboratory using a 32-bit microcomputer system (PC-9821-ST20, NEC Corp., Tokyo, Japan). The LV pressure data at baseline and for four to six points during exercise with and without propranolol infusion were selected for analysis. We calculated the maximum first derivative of LV pressure (LV dP/dt_{max}) as an index of contractility. To evaluate LV isovolumic relaxation, the pressure half-time ($T_{1/2}$) was calculated directly as previously described (7).

Scintigraphic analysis. Perfusion was assessed semiquantitatively, based on analysis of the apical, midventricular and basal short-axis, and vertical long-axis tomograms. The LV

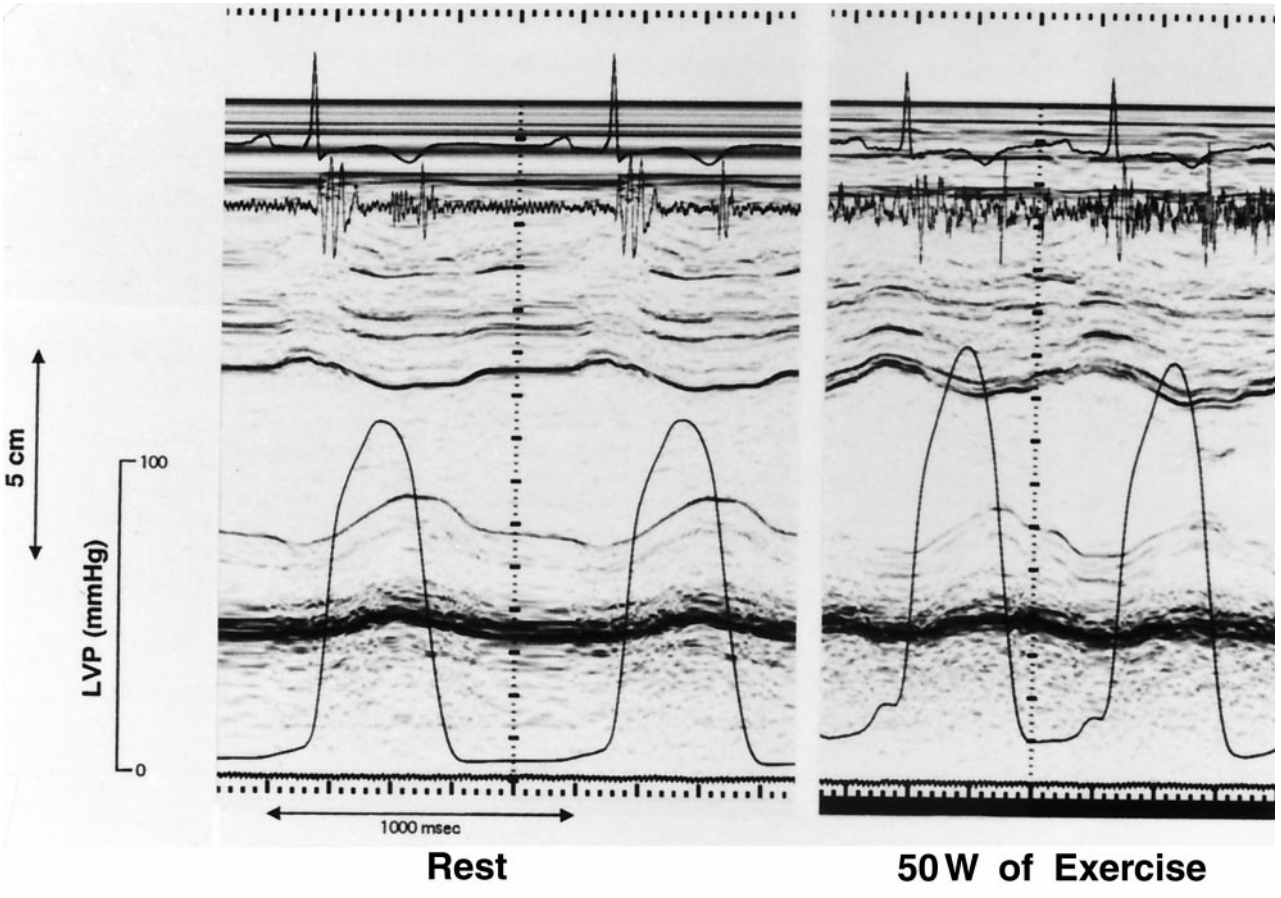

Figure 1. Representative electrocardiograms, phonocardiograms, left ventricular pressure (LVP) tracings, and M-mode echocardiograms at baseline and during 50 W of exercise in a patient with hypertrophic cardiomyopathy.

myocardium was divided into 20 segments (18 from the short-axis images and 2 from the vertical long-axis images). The defect score was defined using a 5-point scale (0 = normal, 1 = equivocal, 2 = mildly reduced perfusion, 3 = severly reduced perfusion, 4 = absent perfusion) by two observers without knowledge of the clinical data (9). The summed stress score and summed rest score were calculated as the sum of scores for the 20 segments for the stress and rest images, respectively. The sum of the differences between the 20 segments from the stress and rest images was defined as the summed difference score (10).

Statistical analysis. Results are expressed as the mean ± SD. One-way factorial analysis of variance (ANOVA) was used to compare baseline characteristics and hemodynamic variables at peak exercise between groups. Within-group comparisons were performed for the hemodynamic changes during exercise by two-way repeated-measures ANOVA. When a significant difference was present, intergroup comparisons were performed using the Scheffé multiple comparison test. The relationships between HR, the percent change for LV dP/dt_{max} and the percent change for $T_{1/2}$ were assessed by the nonlinear least-squares fitting technique. Between-group comparisons of the regression curves were analyzed by analysis of covariance and the Scheffé multiple comparison test. A value of $p < 0.05$ was considered statistically significant. The person who analyzed hemodynamic factors such as $T_{1/2}$ was blinded to the ultimate group assignment and changes in LVEDP.

RESULTS

No complications occurred with the exercise protocol. The total exercise time was 546 ± 109 s in the control group, 540 ± 102 s in group I and 647 ± 84 s in group II. No significant differences occurred in the total exercise time among the three groups. Baseline characteristics and hemodynamic variables during exercise with and without propranolol administration are summarized in Tables 1 and 2.

Baseline data. The interventricular septal thickness was increased in groups I and II, but it was greater in group I than group II (Table 1). The LV hypertrophy score was significantly greater in group I than in group II. Under resting conditions, the LV end-diastolic dimension (EDD) and end-systolic dimension (ESD) did not differ significantly among the three groups (EDD: control, 45.2 ± 2.6 mm; group I, 45.9 ± 4.6 mm; group II, 45.9 ± 3.7 mm. ESD: control, 25.8 ± 4.9 mm; group I, 29.1 ± 5.3 mm; group II, 28.0 ± 2.6 mm). The baseline LVEDP was significantly higher in groups I and II than in the control

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Table 1. Baseline Clinical, Echocardiographic, and Ventriculographic Characteristics of the Patients

	Age (yrs)	IVST (mm)	PWT (mm)	LVH Score	LVEF (%)
Control Group					
1	56	10	10		61
2	68	10	9		78
3	57	11	10		77
4	46	9	9		61
5	59	11	10		57
Mean	57	10	10		67
SD	8	1	1		10
Group I					
6	56	20	12	6	62
7	49	18	12	5	73
8	47	22	20	8	60
9	64	18	12	7	72
10	57	26	18	9	87
11	49	20	12	6	78
12	55	18	11	5	55
13	61	15	10	5	81
14	37	15	10	5	70
15	37	28	13	7	74
16	55	25	10	7	77
Mean	52	20*	13*	6	72
SD	9	4	3	1	9
Group II					
17	38	19	10	5	59
18	50	15	11	5	63
19	47	17	10	3	62
20	51	16	12	5	73
21	56	16	9	5	71
22	60	17	13	5	65
23	56	15	10	3	71
24	45	16	12	3	71
25	54	18	11	3	85
Mean	51	17*†	11*	4†	69
SD	7	1	1	1	8

*$p < 0.05$ vs. control group; †$p < 0.05$ vs. group I.
IVST = interventricular septal thickness; LVEF = left ventricular (LV) ejection fraction; LVH = LV hypertrophy; PWT = posterior wall thickness; SD = standard deviation.

group. The baseline $T_{1/2}$ was significantly longer in groups I and II than in the control group.

Responses to dynamic exercise. Exercise increased HR to a similar extent in all three groups (Table 2). Changes in right atrial pressures and mean arterial pressure, two indicators of changes in preload and afterload, and LV peak systolic pressure also increased to a similar extent in all three groups during exercise. In contrast, the evolution of LVEDP was different in all three groups during exercise. In the control group, the LVEDP reached a plateau value at a HR of 80 beats/min. However, in group I, the LVEDP increased progressively and continuously (Fig. 2). The absolute increase in LVEDP was significantly greater in group I than in the control group (16 ± 5 mm Hg vs. 8 ± 3 mm Hg, respectively). In group II, the changes in LVEDP showed a biphasic pattern, with an initial increase (27 ± 5 mm Hg) up to the critical HR followed by a progressive decline back to the baseline value (16 ± 3 mm Hg) (Fig. 3). The critical HR ranged from 92 to 106 beats/min (mean: 98 ± 4 beats/min). The percent change in the LV dP/dt_{max} followed the increase in HR; the increase in LV dP/dt_{max} at peak exercise was the greatest in group II (124 ± 48%). The increase in LV dP/dt_{max} at the critical HR in group II was much less than that at peak exercise in group I, whereas the LVEDP was similar. The $T_{1/2}$ decreased progressively during exercise in all groups (Fig. 4). However, changes in $T_{1/2}$ in the control group (−36 ± 11%) and in group II (−28 ± 10%) were greater than in group I (−15 ± 10%, both, $p < 0.05$). At 50 W of exercise, in the control group, neither EDD nor ESD significantly changed (EDD: from 45.2 ± 2.6 to 45.8 ± 2.3 mm; ESD: from 25.8 ± 4.9 to 24.2 ± 4.6 mm). In contrast, in group I and in group II, both EDD and ESD decreased significantly (group I: EDD: from 45.9 ± 4.6 to 42.0 ± 4.9 mm, $p < 0.05$; ESD: from 29.1 ± 5.3 to 26.1 ± 6.2 mm, $p < 0.05$. Group II: EDD: from 45.9 ± 3.7 to 42.9 ± 4.3 mm, $p < 0.05$; ESD: from 28.0 ± 2.6 to 24.3 ± 3.0 mm, $p < 0.05$).

Responses to exercise after propranolol infusion. At baseline, after propranolol infusion, the LV peak systolic pressure and LV dP/dt_{max} at baseline were significantly reduced (both $p < 0.05$), the $T_{1/2}$ decreased slightly but the LVEDP was unchanged. During exercise, in group II, the biphasic pattern of changes in the LVEDP disappeared and was replaced by a progressive increase up to peak exercise (Fig. 3); the decrease in $T_{1/2}$ was attenuated.

Scintigraphic findings. Both HR and systolic arterial pressure at peak exercise were similar in groups I and II during exercise ^{201}Tl scintigraphy (HR: 137 ± 12 vs. 136 ± 8 beats/min; systolic arterial pressure: 213 ± 32 vs. 205 ± 29 mm Hg, respectively). Ten of the 11 patients (91%) in group I and 4 of the 9 patients (44%) in group II had abnormal myocardial ^{201}Tl uptake during exercise ($p < 0.01$). Furthermore, 10 of the 11 patients (91%) in group I and 3 of the 9 patients (33%) in group II had reversible myocardial perfusion defects ($p < 0.01$). The summed stress score was significantly greater in group I than in group II (13.5 ± 4.6 vs. 8.3 ± 4.0, $p < 0.05$), whereas the summed rest score was similar in groups I and II (5.6 ± 3.2 vs. 5.3 ± 3.1). The summed difference score was significantly greater in group I than in group II (8.0 ± 4.4 vs. 3.0 ± 2.2, $p < 0.01$). Therefore, patients in group I had more exercise-induced defects and reversible defects than group II patients, suggesting a lower ischemic burden in group II.

Changes in plasma catecholamine concentrations. Exercise induced increases in the plasma concentrations of norepinephrine in all three groups. However, no significant differences were seen in the plasma concentrations of norepinephrine at rest (control, 251 ± 40 pg/ml; group I, 224 ± 115 pg/ml; group II, 237 ± 47 pg/ml) or at peak exercise (control, 926 ± 354 pg/ml; group I, 713 ± 190 pg/ml; group II, 839 ± 263 pg/ml).

Table 2. Hemodynamic Variables at Baseline, at Critical Heart Rate, and at Peak Exercise During Dynamic Exercise and Propranplol Infusion

	Exercise			Exercise With Propranolol (Group II, n = 4)	
	Baseline	Critical HR	Peak Exercise	Baseline	Peak Exercise
Heart rate (beats/min)					
Control group	69 ± 16		119 ± 6* (81 ± 45%)		
Group I	71 ± 12		125 ± 10* (79 ± 30%)		
Group II	69 ± 8	98 ± 4* (44 ± 17%)	129 ± 11*§ (90 ± 27%)§	64 ± 5	120 ± 6‖ (88 ± 16%)
MAP, mm Hg					
Control group	98 ± 23		126 ± 23* (28 ± 10 mm Hg)		
Group I	110 ± 15		133 ± 22* (22 ± 11 mm Hg)		
Group II	104 ± 15	112 ± 15 (9 ± 4 mm Hg)	124 ± 19* (21 ± 15 mm Hg)§	96 ± 18*	108 ± 15‖ (12 ± 4 mm Hg)
LVPSP, mm Hg					
Control group	143 ± 22		188 ± 22* (45 ± 9 mm Hg)		
Group I	145 ± 21		190 ± 34* (45 ± 23 mm Hg)		
Group II	135 ± 23	161 ± 25* (26 ± 8 mm Hg)	181 ± 29* (46 ± 19 mm Hg)§	131 ± 22*	142 ± 22‖¶ (11 ± 4 mm Hg)¶
LVEDP, mm Hg					
Control group	5 ± 3		13 ± 2* (8 ± 3 mm Hg)		
Group I	12 ± 5†		28 ± 8*† (16 ± 5 mm Hg)†		
Group II	14 ± 4†	27 ± 5* (14 ± 4 mm Hg)	16 ± 3‡§ (3 ± 4 mm Hg)‡§	16 ± 2	26 ± 4‖¶ (10 ± 4 mm Hg)¶
LV dp/dt_{max}, mm Hg/s					
Control group	2,121 ± 325		4,017 ± 437* (92 ± 28%)		
Group I	1,904 ± 228		3,373 ± 587* (77 ± 26%)		
Group II	2,161 ± 400	2,908 ± 506 (35 ± 14%)	4,855 ± 1,417*‡§ (124 ± 48%)‡§	1,825 ± 154*	2,848 ± 319‖¶ (56 ± 11%)¶
LV dp/dt_{min}, mm Hg/s					
Control group	−2,256 ± 260		−3,281 ± 293* (−46 ± 23%)		
Group I	−1,728 ± 348†		−2,798 ± 783* (−61 ± 23%)		
Group II	−2,062 ± 437	−2,733 ± 556* (−33 ± 10%)	−3,687 ± 852*‡§ (−81 ± 37%)†§	−1,911 ± 406	−2,436 ± 543‖¶ (−28 ± 8%)¶
$T_{1/2}$ (ms)					
Control group	33 ± 3		21 ± 4* (−36 ± 11%)		
Group I	47 ± 4†		40 ± 5*† (−15 ± 10%)†		
Group II	44 ± 4†	39 ± 3* (−11 ± 6%)	31 ± 4*†‡§ (−28 ± 10%)‡§	42 ± 2	39 ± 3‖¶ (−8 ± 4%)¶
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)					
Control group	2.7 ± 0.5		6.4 ± 1.4* (150 ± 89%)		
Group I	2.9 ± 0.4		6.1 ± 1.3* (117 ± 67%)		
Group II	3.0 ± 0.3	4.6 ± 0.6* (54 ± 19%)	7.0 ± 1.0*§ (137 ± 43%)§	2.8 ± 0.8	5.6 ± 0.5¶ (111 ± 68%)
PAWP, mm Hg					
Control group	6 ± 2		16 ± 5* (10 ± 3 mm Hg)		
Group I	8 ± 3		27 ± 8*† (19 ± 6 mm Hg)†		
Group II	9 ± 4	19 ± 3* (10 ± 4 mm Hg)	21 ± 5*‡ (11 ± 7 mm Hg)‡	12 ± 1	27 ± 5‖¶ (15 ± 5 mm Hg)¶
MRAP, mm Hg					
Control group	3 ± 2		6 ± 3 (3 ± 2 mm Hg)		
Group I	4 ± 2		8 ± 3* (4 ± 2 mm Hg)		
Group II	4 ± 2	8 ± 2* (4 ± 1 mm Hg)	8 ± 2* (4 ± 2 mm Hg)	4 ± 5	7 ± 6 (3 ± 4 mm Hg)

*$p < 0.05$ vs. baseline. †$p < 0.05$ vs. control. ‡$p < 0.05$ vs. group I. §$p < 0.05$ vs. critical HP. ‖$p < 0.05$ vs. baseline during propranolol infusion. ¶$p < 0.05$ vs. peak exercise without propranolol infusion. Numbers in parentheses are percent change from baseline or increment from baseline (MAP, LVPSP, LVEDP, PAWP, and MRAP).

LVEDP = left ventricular end-diastolic pressure; LVPSP = left ventricular peak systolic pressure; MAP = mean arterial pressure; MRAP = mean right atrial pressure; PAWP = pulmonary artery wedge pressure.

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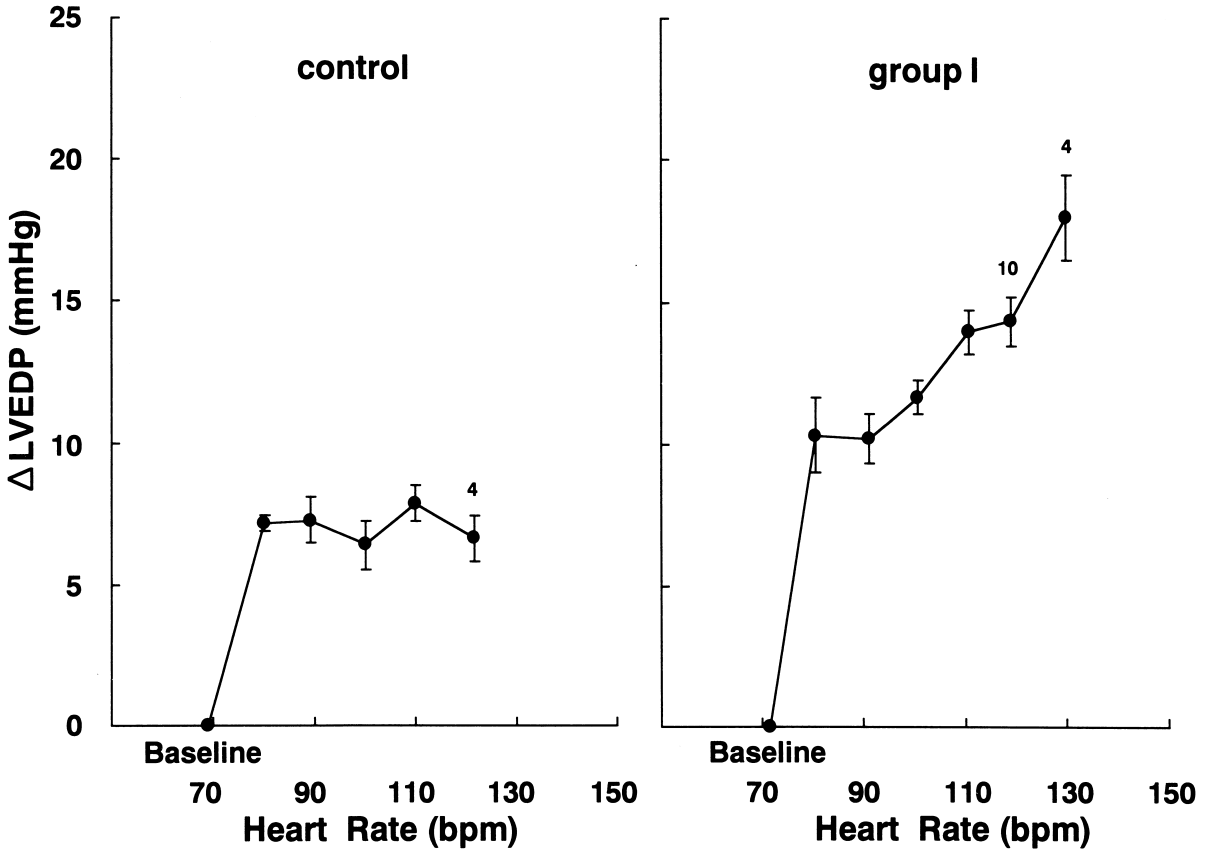

Figure 2. Relationships between heart rate and ΔLVEDP (increment from baseline) during dynamic exercise in the control group **(left)** and group I **(right)**. Numbers represent the number of patients analyzed. LVEDP = left ventricular end-diastolic pressure.

DISCUSSION

The most novel observation in the present study is that there were two distinct patterns of exercise-induced changes in the LVEDP in patients with HCM. The LVEDP steadily increased throughout exercise in patients with relatively severe HCM (group I). In contrast, the LVEDP exhibited biphasic changes in patients with mild to moderate HCM (group II). Importantly, the LVEDP at peak exercise in group I was similar to that at the critical HR in group II patients.

Exercise-induced changes in hemodynamics. The exercise-induced augmentation of venous return, as reflected by changes in mean right atrial pressures, was similar in groups I and II. In addition, exercise increased the mean arterial pressure, an indicator of LV afterload, to a similar extent in groups I and II. Although it was reported that exercise-induced hypotension occurred in 33% of patients with HCM (11), abnormal hypotension was not observed in any subject studied. Furthermore, LVEDP at peak exercise was lower in group II than group I patients. Therefore, the prominent increase in LV systolic performance during exercise in group II cannot be ascribed to changes in LV loading conditions (i.e., Frank-Staring mechanism), suggesting the augmented LV contractility itself during dynamic exercise in group II. Hittinger et al. (12) have reported that hemodynamic responses to exercise depend upon the severity of LV hypertrophy. Furthermore, we observed that the reduction in $T_{1/2}$ in patients in group II was greater than in group I patients. The LV functional reserve during exercise may be preserved in patients with lesser amounts of LV hypertrophy.

The LVEDP can be elevated without an increase in LV end-diastolic volume because of diminished ventricular compliance or alterations in the LV pressure-volume relationship in the setting of ischemia, hypertrophy, fibrosis and infiltrative diseases of the ventricle and pericardial disease (2,3). The fact that LVEDP decreased after critical HR in group II despite similar LV internal dimensions in both groups might indicate the substantial improvement of LV compliance in group II patients.

Myocardial ischemia. Myocardial ischemia plays an important role in the pathophysiology and natural history of HCM. Previous studies have demonstrated that myocardial perfusion defects commonly develop during exercise in asymptomatic and minimally symptomatic patients with HCM (13–17). Thallium 201 scintigraphic myocardial defects in patients with HCM have been repetitively described (13–15). Therefore, our data suggest that there was a lower ischemic burden in group II patients than in group I patients.

The exact mechanisms responsible for myocardial ischemia in HCM are not known. However, an increase in

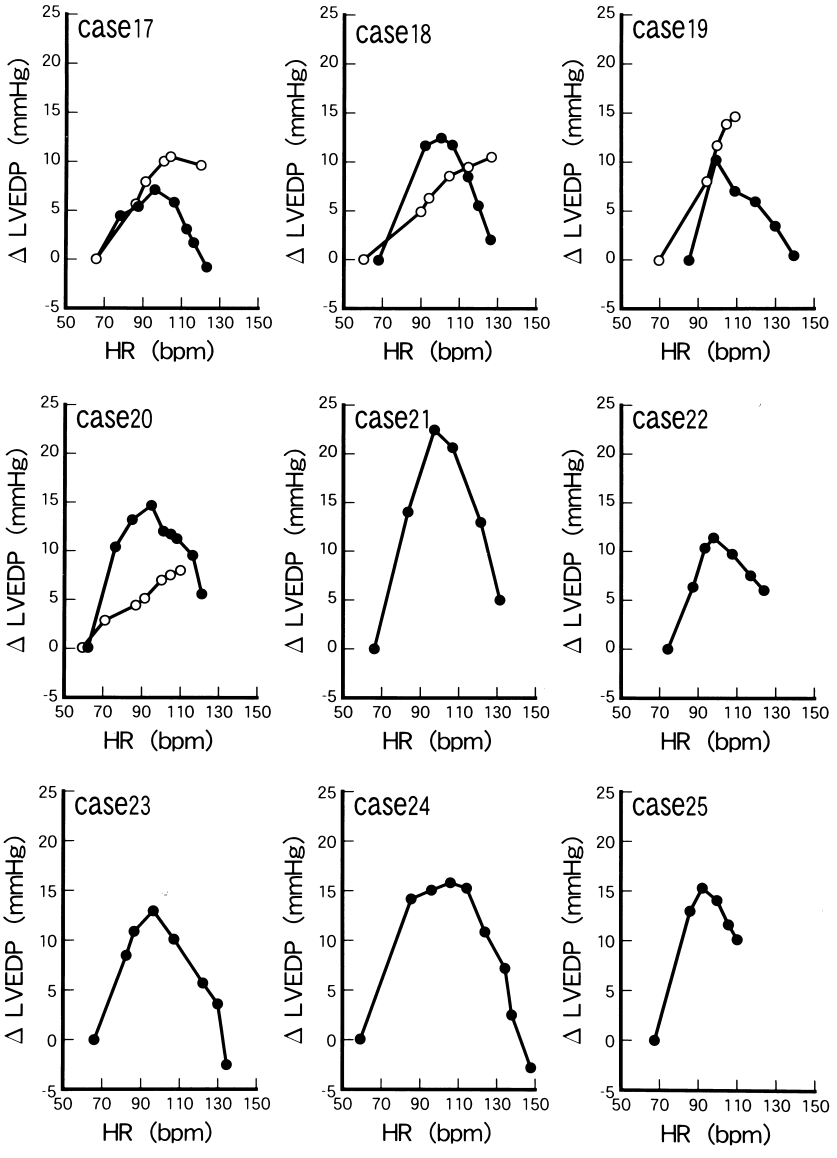

Figure 3. Relationships between heart rate (HR) and ΔLVEDP (increment from baseline) during dynamic exercise before **(filled circle)** and after **(open circle)** propranolol administration in group II patients. LVEDP = left ventricular end-diastolic pressure.

myocardial oxygen demand beyond the capacity of a vascular bed that has not grown in proportion to the degree of LV hypertrophy, abnormal coronary reserve caused by elevated LV filling pressures, or abnormalities of the small intramural coronary arteries may be responsible (14–20). Structural and functional alterations in the intramural coronary arteries would be expected to be responsible, at least in part, for myocardial ischemia (18–20), and an abnormal increase in LVEDP during exercise in group I patients. In contrast, small intramural coronary artery reserve may not be as severely impaired in group II patients.

Mechanisms of biphasic LVEDP changes. Udelson et al. (21) have demonstrated that beta-adrenergic stimulation with isoproterenol enhances LV relaxation and improves diastolic pressure-volume relations in HCM compared with the pacing tachycardia to the same HR. Their results suggested that the adverse effect of ischemia on LV relaxation might be alleviated by beta-adrenergic stimulation in patients with HCM. Dynamic exercise may have deleterious effects in patients with severe HCM by increasing HR and contractility, thereby augmenting myocardial oxygen demand and aggravating myocardial ischemia. However, dynamic exercise might also have favorable effects by facilitating LV relaxation and filling through changes in loading conditions and coronary vascular tone in patients with mild HCM.

One of the potential mechanisms of the biphasic LVEDP changes might be an improved coronary circulation modulated by exercise-induced beta-adrenergic stimulation. The coronary arteries are richly innervated by beta-adrenergic nerves, and their activation can exert coronary vasodilation. However, beta-blockade-induced coronary vasoconstriction

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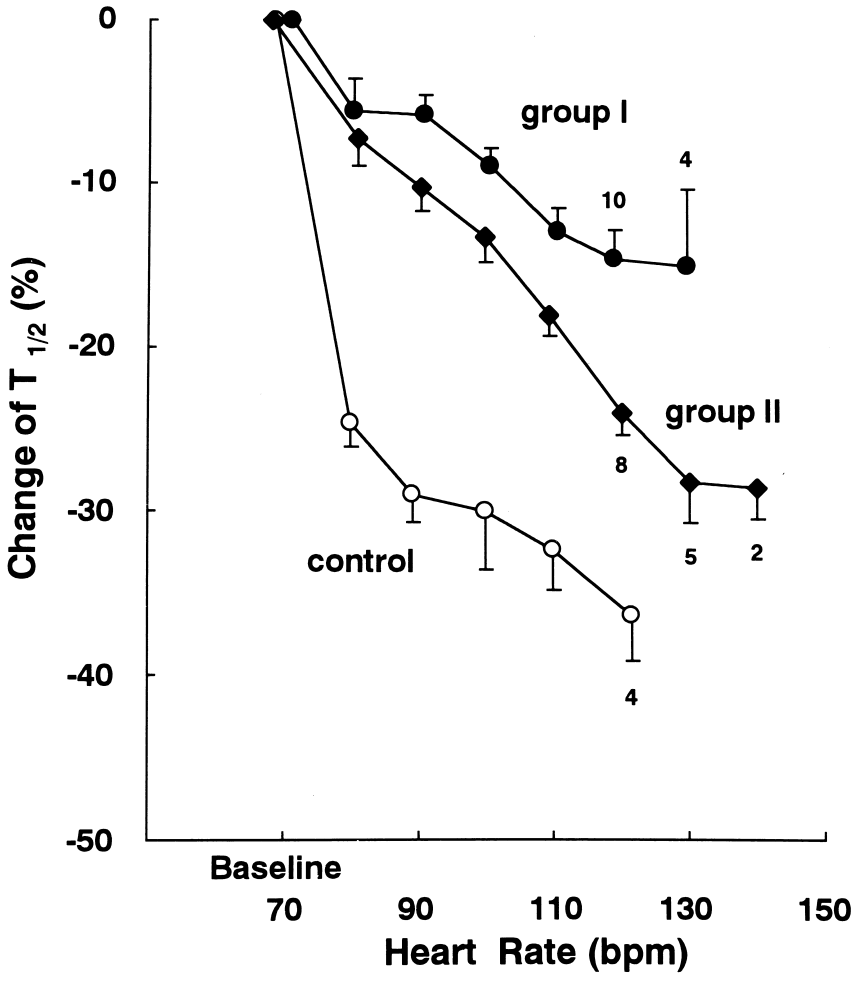

Figure 4. Relationships between heart rate and the time constant of isovolumic relaxation ($T_{1/2}$, normalized as the percentage of the value at baseline heart rate) during dynamic exercise in the control group **(bottom)**, group I **(upper)**, and group II **(middle)**. Numbers represent the number of patients analyzed.

has been demonstrated to be primarily due to a lower metabolic demand (22). Neurally and hormonally mediated vasoconstriction can be overwhelmed by metabolic vasodilation during exercise in normal conscious dogs (23). In the present study, the exercise-induced biphasic LVEDP changes in group II patients disappeared after administration of propranolol. Taken together, beta-adrenergic activation may play a significant role in the biphasic changes in LVEDP during dynamic exercise.

Conclusions. Finally, two distinct patterns of exercise-induced changes in LVEDP can be observed in patients with HCM. The LVEDP steadily increased throughout exercise in patients with severe HCM. In contrast, LVEDP increased initially and then declined during exercise with concomitant improvement in LV performance in patients with mild to moderate HCM. The metabolic vasodilation induced by beta-adrenergic activation might have favorable effects on LV performance in patients with mild HCM. The biphasic changes in LVEDP seen during exercise might be related to improved coronary microcirculation in response to beta-adrenergic stimulation in patients with mild to moderate HCM.

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